A discussion:

L1-ELEMENTS ACTIVITY AND CO-EXPRESSION OF SIGNALING MODULES IN A SINGLE CANCER CELL

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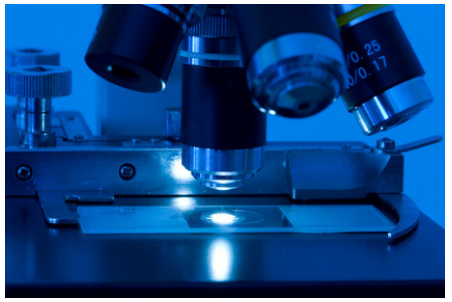
Cancer cells have mutations, methylation pattern and expression profiling other than in normal cells. A crucial part of cancer studies is to investigate how these distinguish lead to cancer. L1-elements can produce chimeric transcripts and activate non-coding RNA clusters. If L1s play such a role in cancer then we are at a tip of iceberg in understanding of mechanisms of this disease.

- **Philosophy**: compositional evolution and modularity
- **Approach**: recognition of modules and their combinations
- **Examples**
  - Modular distribution of sulfur metabolism genes in bacterial populations
  - Behavior of L1-elements in the human genome
- **The point**: perspectives of new technologies and applications for individual cells

Universität Regensburg, 30.05.11

Microbial world vs. Cancer



What is in common?

- Complexity is a result of combinatorial explosion. The cellular circuitry is not infinitely complex. Hopefully, the number of modules is to be tractable
- Reuse of modules is fundamental for evolvability

What is different?

- The scale of systems (macroscopic vs. microscopic)
- The mechanisms of evolution (exchange by structural genes vs. mobilization of controlling elements)

A set of good skeptical questions

- How could we manage complexity?
- How can one explain sudden transitions in the evolution process?

Modularity and interchangeable communication between modules

"Module is a set of genes that act together to carry out a specific function"

- Try to find modules, relations between modules, the origin of modules.
- Try to understand the hierarchy of a modular system and a reason of the entanglement within modules and between modules.

'Harlequin's Carnival'
Joan Miró (1924-1925)

A hope

The answer following questions could have given a key to control an evolution process (in cancer):

- How does a system evolve and fall?
- What is a limit of evolvability?

Sulfur metabolism in bacterial populations

Reference: BLAST(*Thiomicrospira crunogena*, *Thiobacillus denitrificans*, *Vesicomyosocius okutanii*, *Ruthia magnifica*) TO (CAMERA)

Gene identification: KEGG(sulfur metabolism) TO (*V.okutanii*)

Search in databases: BLAST(21 sulfur genes from *V.okutanii*) TO (CAMERA)

Astonishing result:

The possible lateral gene transfer affected 16S rRNA phylogeny.

Most important conclusion:

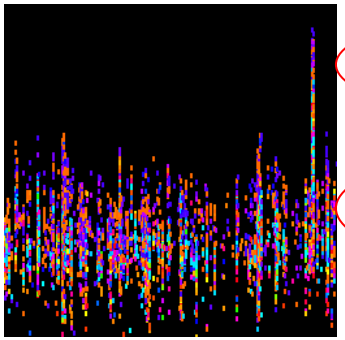
The lateral gene transfer supports the modularization on the global scale.

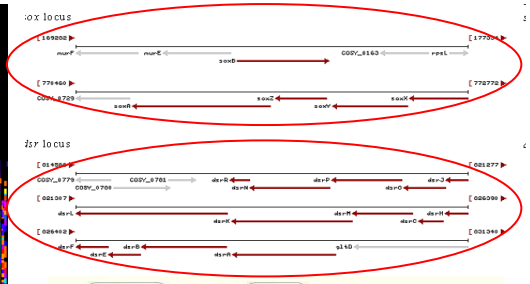
Corollary:

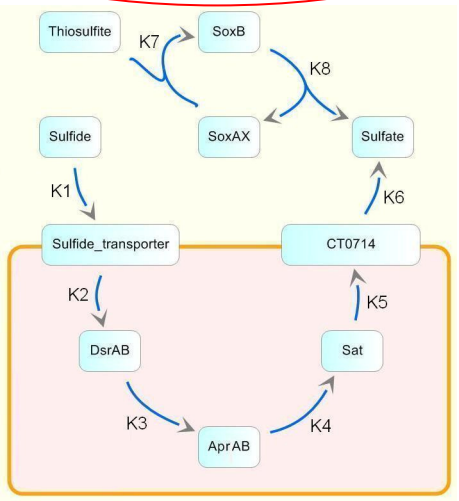
Recombinations provides modularization in protein structures.

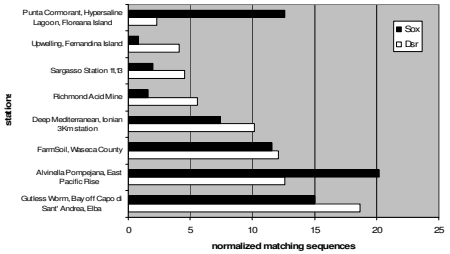
Methodology:

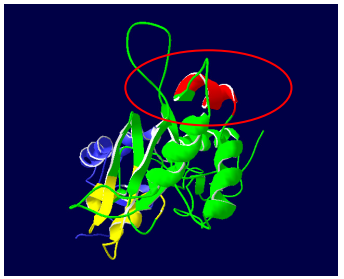
- simplification of the inferred metabolic system
- models describing a role of the substrate transport in different languages

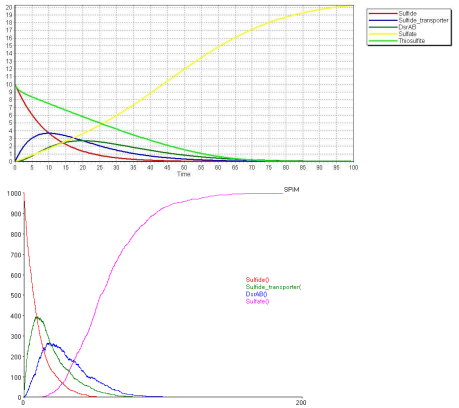












(Kuznetsov, 2010)

Human genome and transcriptome

‘Where Do We Come From? What Are We? Where Are We Going?’
Paul Gauguin (1897–1898)

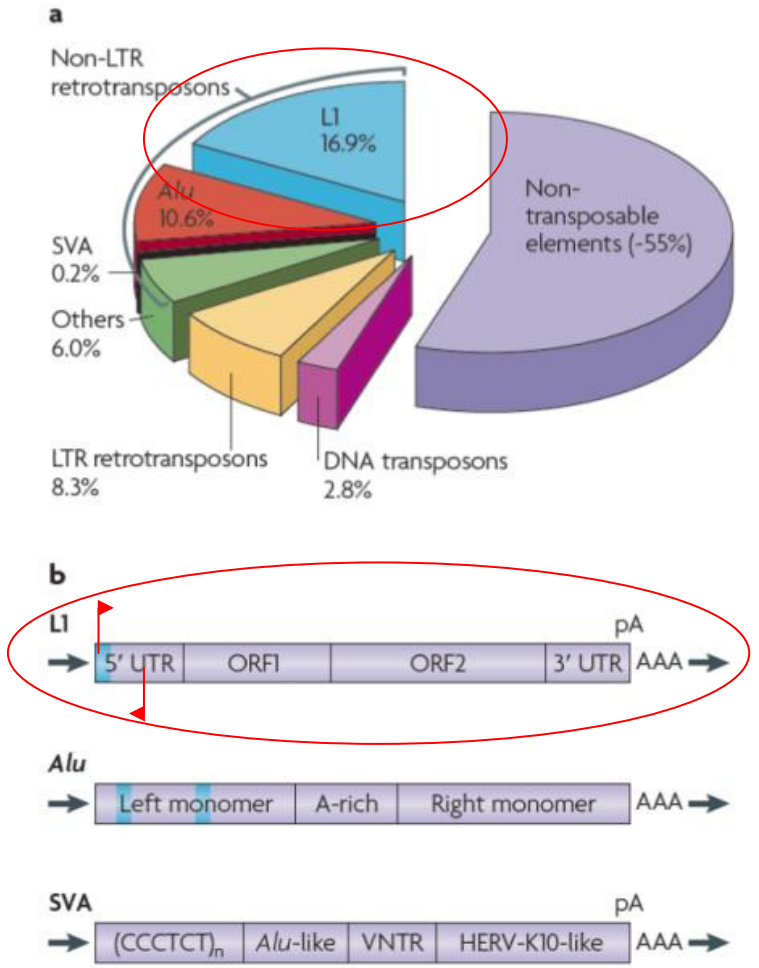
- How did humans evolve?
- How they have been evolved?

- The space of possibilities is huge. One should reduce it.
- Everyone can do this job in a different way.
- Consider L1-elements, for example.

L1-elements

- There're >500,000 L1 copies that constitute ~17% of the human genome.
- They arrived 150 Myr ago possibly by HGT, expanded ancestor genome using TPRT and still transmitted by VGT.
- They play a significant role in the genomic instability, early development, brain plasticity and cancerogenesis because they can provoke homologous recombination and co-transcription of the non-coding and coding RNAs.

They are critical "controlling elements".



(Cordaux, Batzer, 2009)

Some more facts about L1-elements

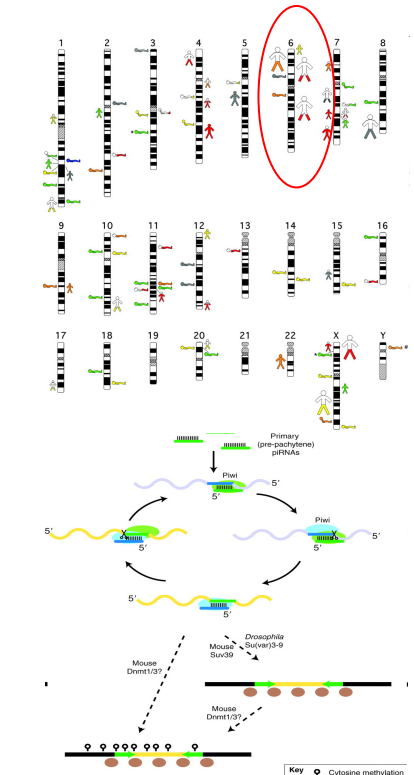
- L1-elements distribution in human genome (Brouha et al, 2003)
- in more aggressive cancers
- in cancer databases (Baba et al, 2010)

Potential cancer biomarkers:

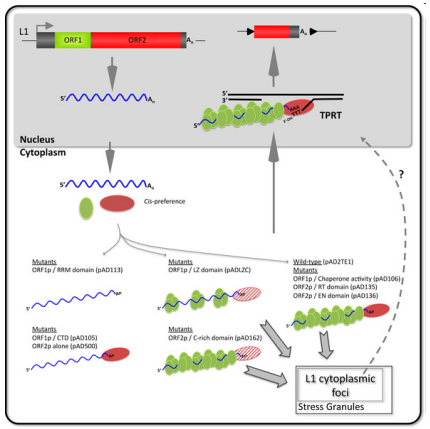
- piRNA expression (MIWI/piRNA pathway)
- hypomethylation (COBRA)

ORF1p and ORF2p are possible targets for the cancer therapy

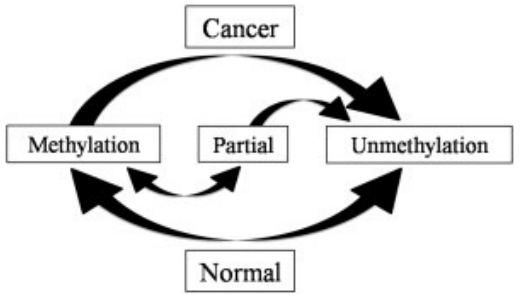
- cystein-rich domain
- RNA recognition motif
- carboxy-terminal domain
- endonuclease activity
- reverse transcriptase activity

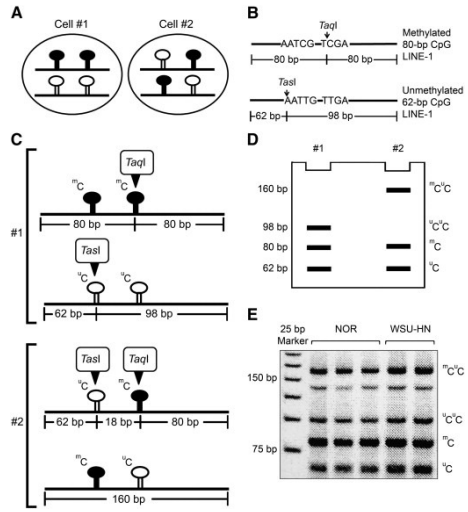


(Wolfswinkel, Ketting, 2010)

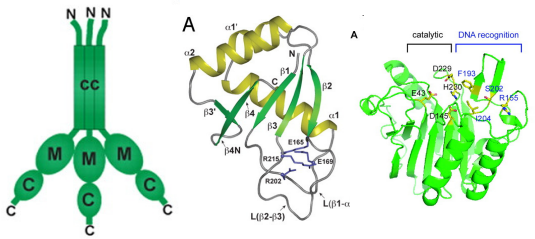


(Doucet et al, 2010)





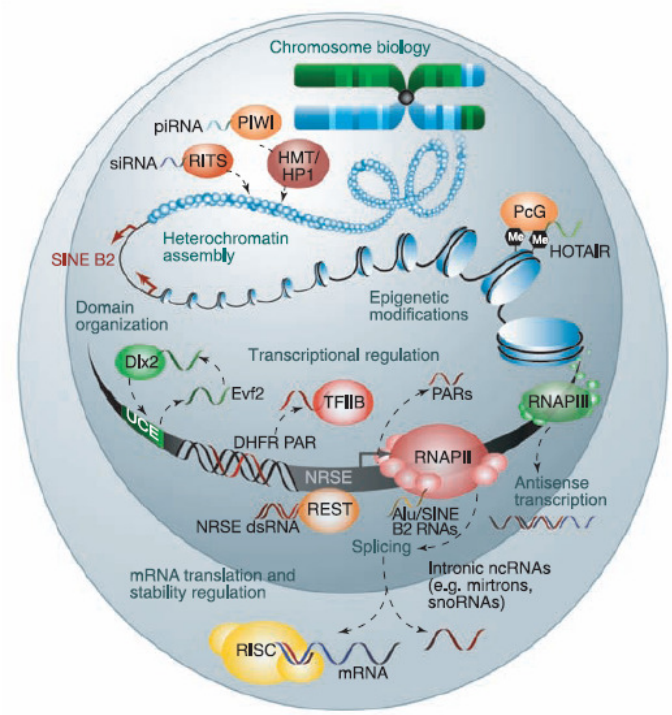
(Pobsook et al, 2010)



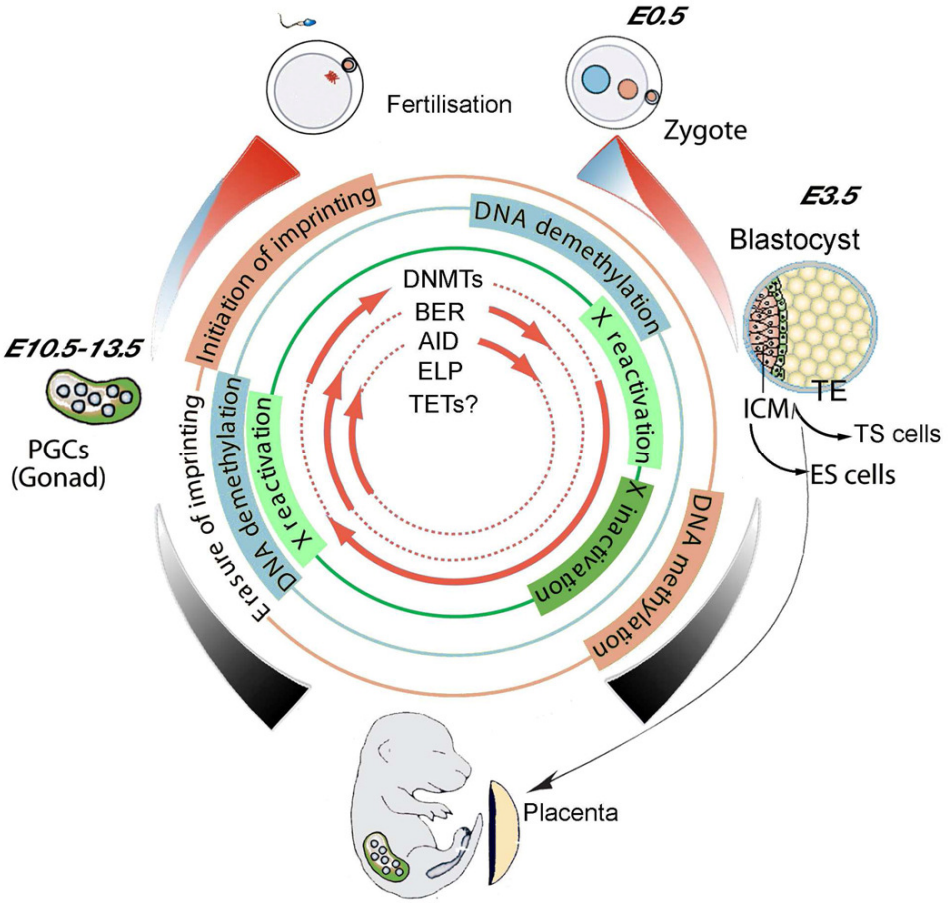
(Khazina, Weichenrieder, 2009)
(Ichiyanagi et al, 2007)

Questions

- Is this a way to manage the cancer evolvability? Possibly, yes!
- How about an interference with internal cellular mechanisms and possible side effects? Maybe yes, maybe not…

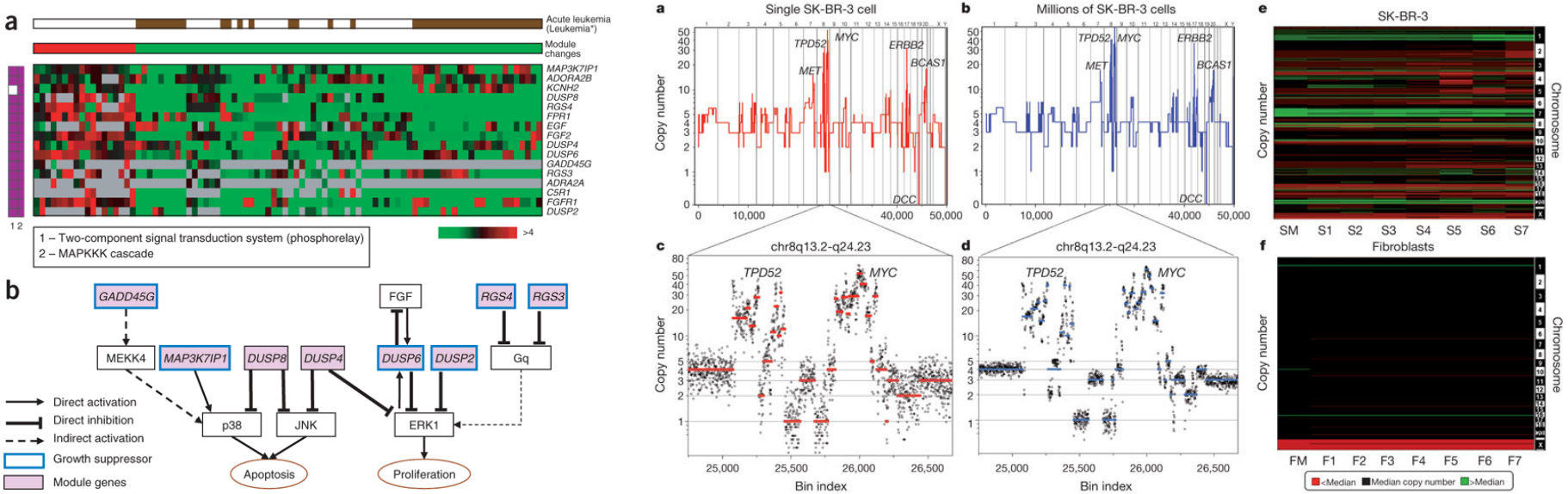


(Amaral et al, 2008)

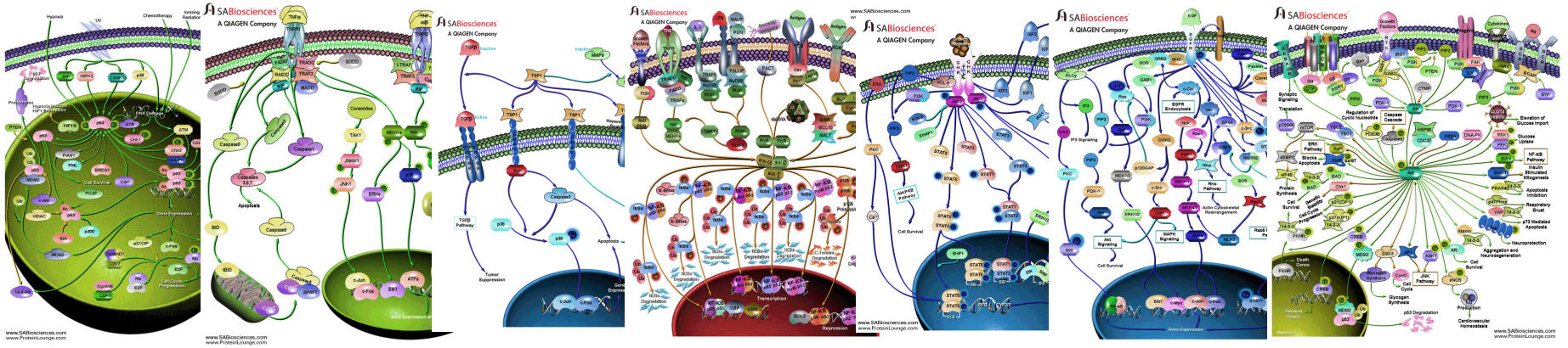


(Feng et al, 2010)

What do new technologies bring?



- Modular co-expression of signaling pathways in cancer (Segal et al, 2004)
- Single cell genome sequencing (Navin et al, 2011)



Whitney cusp surfaces in cancer

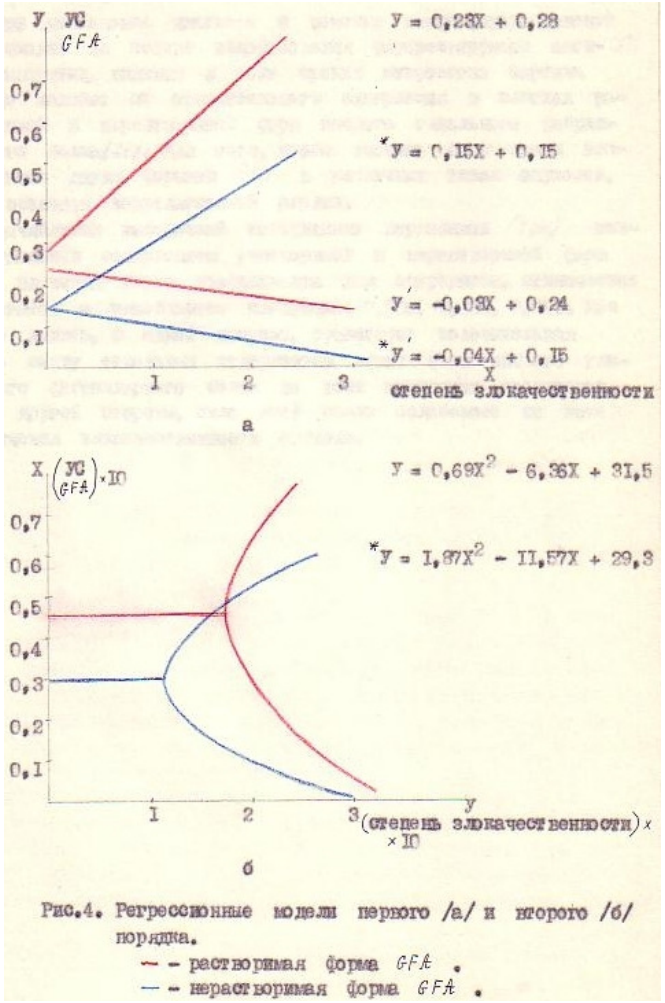
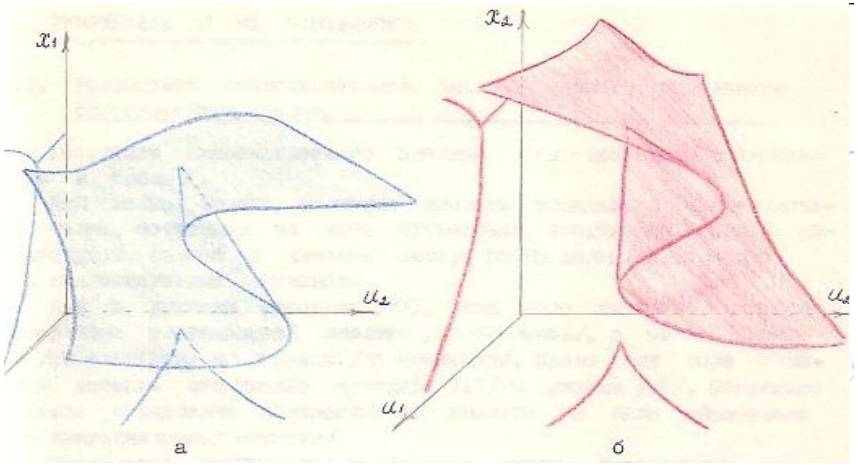


Рис.4. Регрессионные модели первого /а/ и второго /б/ порядка.
— – растворимая форма GFA .
— – нерастворимая форма GFA .



- Distributions of soluble and insoluble forms of GFA protein in the normal and malignant nervous cells are described by the canonical cusp catastrophes.

(Kuznetsova, 1984)

To discussion: "*Transposon activity as a possible modulator of signaling pathways".*

1. Which kind of mutations is most important in cancer? (not only p53 :)
2. Evolvability! What about a "pluripotent potential" of cancer stem cells?
3. Whether L1 elements are driving cancer, or whether L1 transcripts found in tumours are the result of cancer itself?
4. Will a silencing of L1-elements lead to a prevention of cancer? e.g. suppressing the co-transcription of non-coding RNAs which recruit EZH2 from Polycomb complex PRC2
5. Does demethylation of CpG islands correlate with co-expression of "cancer" signaling modules?
6. Which business model is better for cancer: prevention or treatment?
7. Does it make sense to search for stress factors mobilizing L1-elememts and to detect circulating cancer derived DNA/RNA?
8. Whether a reason of cancer evolution is the communication between modules?
9. Are we entering the end game of the anticancer mission?

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